REMARKS

Enclosed is a Notice of Appeal with the necessary fee. Applicant appeals from the Final Rejection mailed on April 16, 2004 rejecting claims 4-15, 18-23, 39-47 and 49-56.

Enclosed please also find in original USPTO's form SB96, Statement Under 37 CFR 3.73(b), and a Statement from the Assignee regarding change of Associate Practitioner in this case.

Status of Claims

Claims 4-15, 18-23, 39-47, 49-56 are pending in the application.

Rejection Under 35 U.S.C. § 112 of Claims 21, 49 and 53-54

The Examiner rejected claims 21, 49 and 53-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, because the Specification fails to contain word "fungicides" as recited in the amended claims.

Applicant would like to draw the Examiner's attention to page 18, first paragraph, line 15 in the Specification, in which the word fungicide is mentioned. The full sentence reads:

> Preferred active agents for use in accordance with the present invention include pigments, dyes, inks, paints, detergents, food sweeteners, spices, adsorbants, absorbents, catalysts, nucleating agents, thickening agents, pesticides, fungicides, disinfectants, perfumes, deodorants, and combinations thereof.

The word fungicide is also mentioned in page 62, second full paragraph, line 28 in the specification. Thus, this rejection should now be withdrawn.

Rejection Under 35 U.S.C. § 103(a) of Claims 4, 8-15, 18-23, 39-47, 49-50 and 55-56

The Examiner rejected claims 4, 8-15, 18-23, 39-47, 49-50 and 55-56 under 35 U.S.C. § 103(a) as being unpatentable over Hanes et al. (US 5855913, cited prior art) in view of Cohen et al. (5149543) by themselves, or in further view of Yen (5308620, cited prior art). This rejection is respectfully traversed.

Claim 39 et al.

Independent claim 39 is to an inhaleable powder composition comprising a plurality of particulate microstructures. The particulate microstructures have (i) a structural matrix comprising an active agent, calcium, and a phospholipid, and (ii) a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

The Examiner states that Hanes et al. teaches aerodynamically light particles for drug delivery to the pulmonary system that have a tap density of less than 0.4 gm/cm^3, the instant aerodynamic diameter, and mass mean diameters between 5 to 30 microns. The Examiner further states that Hanes et al. teaches the use of polyglycolic acid with a surfactant (DPPC) and that the polyester may also have charged or functionizable groups such as amino acids.

Claim 39 has a number of differences with Hanes et al. For example, claim 39 recites a particulate microstructure having a bulk density of less than about 0.5 g/cm^3, which is not the same as Hanes et al's teachings to particles having a tap density of less than 0.4 gm/cm^3. The bulk density of a powder is the weight of the powder per unit of volume compared to the weight of the same volume of water, measured for example, in a graduated cylinder. The tap density of a powder is obtained by repeatedly tapping a vessel containing the powdered material until the volume of the material in the vessel does not further decrease. Thus, measured tap density is affected by the size and shape of the vessel, the amplitude of the taps, the frequency of the tapping, and other factors; while the bulk density measurement is not subjected to these conditions. The flow and rheological

properties of the powder would also affect the tap density value. Thus, a tap density measurement is not the same as a bulk density measurement.

Secondly, claim 39 is to a particulate microstructure having a mean aerodynamic diameter of less than 5 microns. Hanes et al. makes no mention of the importance of mean aerodynamic diameter. A particle population having particles with different shapes, sizes and densities, can be compared in terms of their aerodynamic behavior with a population of ideal particles all having the same mean aerodynamic diameter. Settling techniques in air or liquid, can be used to define the mean aerodynamic diameter of a sample population of particulates as the calculated diameter of ideal particles exhibiting the same aerodynamic behavior as the sample population (as quantified, for example, by their settling speed). As taught by the instant Specification at page 38, lines 14-22:

> Unlike the geometric particle size, the aerodynamic particle size, d_{aer}, of the perforated microstructures depends substantially on the particle density, P : $d_{aer} = d_{geo}\rho$, where d_{geo} is the geometric diameter. For a particle density of 0.1 g/cm^3, d_{aer} will be roughly three times smaller than d_{geo}, leading to increased particle deposition into the peripheral regions of the lung and correspondingly less deposition in the throat. In this regard, the mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 um, ...

Hanes et al. does not teach the desirability of determining the mean aerodynamic diameters of a population of particulate microstructures. Nor does Hanes et al. recognize the desirability of the claimed numerical value of the mean aerodynamic diameter of less than about 5 microns. Instead, Hanes et al. only teaches that the particles are "aerodynamically light particles." A particle can be aerodynamically light with a high volume to density ratio, for example, a structure like a feather is aerodynamically light. However, this is not mean that the feather structure has a mean aerodynamic diameter that is within the claimed range, as suggested by the Examiner's rejection.

Furthermore, Applicant respectfully disagrees that the combination of Hanes et al. and Cohen et al. results in a prima facie obviousness rejection of claim 39. As acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in a

structural matrix. The Examiner states that it would have been obvious to combine the teachings of Hanes and Cohen et al., because Cohen et al. teaches a method of making microspheres based on the use of water-soluble polymers with charged sides that are cross-linked with multivalent cations, such as calcium.

However, neither Hanes et al. nor Cohen et al. teach or suggest the desirability of an inhalable composition comprising particulate microstructures having a structural matrix comprising an active agent, calcium, and a phospholipid, with the desired size ranges, as taught in claim 39.

Hanes et al. teaches forming particles from polymers which are dissolved in a volatile organic solvent, such as methylene chloride. The resultant solution is suspended in an aqueous phase containing a surface active agent, such as PVA, to form an emulsion that is stirred until most of the organic solvent evaporates leaving behind polymer particles. (Hanes et al. Col. 7, lines 17-32.) Hanes et al. does not make any mention of calcium.

Cohen et al. teaches that "the preferred cations for cross-linking of polymers with acidic side groups to form a hydrogel are divalent and trivalent cations such as copper, calcium...." (Col 6, lines, 21-24). Thus, Cohen et al. teaches polymers that are not the same as the polymer taught by a Hanes et al. because the preferred polymers taught by Hanes et al. are not the water-soluble polymers with charged side chains taught by Cohen et al.

Thus, one of ordinary skill in the art would not have found it obvious to modify Hanes et al based on the teachings of Cohen et al. Specifically, one of ordinary skill in the art would have no reason to selectively extract the calcium taught by Cohen et al. and insert this calcium into the polymers taught by Hanes et al.

Furthermore, Hanes et al. teaches against the cited combination. The organic solvent dissolved polymer of Hanes et al. is suspended in an aqueous medium containing a surface active agent, such as PVA, to form an emulsion that is stirred until the

organic solvent evaporates to leave behind particles. If the Hanes et al. composition were cross-linked with the addition of calcium, the resultant composition, could form a contiguous sheet of material or other such contiguous structures, and not discrete separable particles having the sizes described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences, that Hanes et al. teaches against forming a continuous structure having cross-linked bonds.

The Examiner further cites Yen but does not state the basis upon which Yen is relied upon. Yen teaches a method of producing nanomatrixes comprising different proteins, mixed with a solution comprising an organic solvent, such as alcohol. The resultant turbid suspension of monodispersed nanomatrixes are stable against aggregation, and biologically active substance can be added to the solution. Yen does not teach an inhaleable powder composition comprising a plurality of particulate microstructures having a structural matrix comprising an active agent, calcium, and a phospholipid. Nor does Yen teach that the particulate microstructures should have a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3. Thus, Yen does not remedy the deficiencies of Hanes et al. and Cohen et al..

Claims 4-15, 18-23, 52, 53 and 55 depend upon claim 39, and are not rendered unpatentable by the cited references for the same reasons as claim 39, from which they depend. In addition, these claims recite additional distinguishing features. For example, claim 4 recites that the microstructures are porous. Claim 12 recites that the microstructures are hollow and porous. Claim 15 recites that the mean geometric diameter is less than about 5 microns.

For these reasons, claim 39 and its dependent claims are not rendered unpatentable by Hanes et al., Cohen et al., or the combination further in view of Yen. Accordingly, the Examiner is respectfully requested to allow claim 39 and against dependent therefrom.

Claim 40 et al.

Independent claimed 40 is also not rendered unpatentable by Hanes et al., Cohen et al., or the combination further in view of Yen.

Claim 40 is to an inhalable powder composition comprising a plurality of particulate microstructures that include a structural matrix comprising calcium, an active agent, and a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C. As discussed above, Hanes et al. does not disclose a particulate microstructure comprising calcium, an active agent, and a phospholipid. Cohen et al. does not make up for the deficiencies of Hanes et al. because Cohen et al. does not teach polymers used by Hanes et al. thereby providing no motivation to combine the calcium the taught by Cohen et al. with Hanes et al. polymers. Moreover, the combination is also defective since Hanes teaches formation of discrete particles from the polymers, which would not occur if the polymers are cross-linked by calcium, as taught by Cohen et al. Nor does Yen provide the motivation to fill the deficiencies of the Cohen et al. and Hanes et al. combination, because Yen does not teach or suggest the claimed combination of calcium, an active agent, and phospholipid, in the particulate microstructures.

Moreover, the cited references also do not teach particulate microstructures that not only include a structural matrix comprising calcium an active agent, and a phospholipid, but that also recite that the selected phospholipid should have a gel to liquid crystal transition temperature of greater than 40°C. That it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, is not taught are suggested by the cited references. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, claim 40 and the claims dependent therefrom, are not rendered unpatentable by Hanes et al., Cohen et al., or the combination further in view of Yen.

Rejection Under 35 U.S.C. § 103(a) of Claims 5-7

The Examiner rejected claims 5-7 as being unpatentable over Hanes et al (US 5855913, cited prior art) in view of Cohen et al (5149543) in further view of Yen (5308620, cited prior art). This rejection is respectfully traversed.

Claims 5-7 depend upon claim 39, and are patentable for the same reasons as claim 39, from which they depend, as stated above. In addition, these claims recite additional distinguishing features. For example, claim 5 recites that the particulate microstructures have a porosity of 2-40%. Claim 6 states that the microstructures are porous and have a mean pore size of 20-200 nm. Claim 7 further states that the mean pore size is 50-100 nm. The desirability of these ranges of porosity or mean pore size distribution, in combination with a particulate microstructure comprising an active agent, calcium and a phospholipid, is not suggested in the cited combination of references.

As explained above, Hanes et al. teaches forming discrete particles by evaporating an aqueous solution comprising a solvent and polymer, and thus teaches against cross-linking the polymer in the solvent, which would result in a continuous structure and not discrete particles. Hanes is silent on any teaching to calcium, and teaches against the desirability of adding calcium for the reasons taught by Cohen et al., namely that calcium is added to cross-linked polymer. Yen also does not teach or suggest a particulate microstructure comprising the claimed combination of elements.

For these reasons, the Examiner respectfully requested to allow claims 5-7 over the cited references.

Rejection Under 35 U.S.C. § 103(a) of Claims 51-52

The Examiner rejected claims 51-52 as being unpatentable over Hanes et al (US 5855913) in view of Cohen et al (5149543) in further view of Igarashi et al. (4201774). This rejection is respectfully traversed.

Claims 51 and 52 are to an inhalable powder composition in which bioactive agent is an aminoglycoside antibiotic. Claims 51 and 52 are dependent upon claims 40 and 39, respectively, and consequently, are not rented unpatentable for the same reasons as claims 40 and 39, from which they depend. Specifically, neither Cohen et al. nor Igarashi teach or suggest a particulate microstructure comprising the claimed combination of aminoglycoside antibiotic active agent, calcium, and phospholipid, in combination with recited particles sizes in claim 39, or in combination with a phospholipid having a gel to liquid crystal transition temperatures as in claim 40.

For these reasons, the Examiner respectfully requested to allow claims 51 and 52 over the cited references.

Rejection Under 35 U.S.C. § 103(a) of Claims 53-54

The Examiner rejected claims 53-54 as being unpatentable over Hanes et al (US 5855913) in view of Cohen et al (5149543) in further view of Benson et al (5,006,343). This rejection is also respectfully traversed.

Claims 53 and 54 are to an inhaleable powder composition as stated in claims 39 and 40, respectfully, and further include a bioactive agent that is a fungicide. Claims 53 and 54 depend upon claims 39 and 40, respectively, and consequently, are not rendered unpatentable for the same reasons as claims 40 and 39, from which they depend. Neither Cohen et al. nor Igarashi teach or suggest a particulate microstructure comprising the claimed combination of fungicide, calcium, and phospholipid, in combination with recited particles sizes as in claim 39, or in combination with a phospholipid having a gel to liquid crystal transition temperatures as in claim 40.

For these reasons, the Examiner respectfully requested to allow claims 53 and 54 over the cited references.

CONCLUSION

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES, P.C.

Date: October 18, 2004 By: _____

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